

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE FORM PTO-1390 (REV 10-2000)		ATTORNEY'S DOCKET NUMBER PF 84 PCT US ju
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) <b>09/743248</b>
INTERNATIONAL APPLICATION NO. PCT/FR99/01614	INTERNATIONAL FILING DATE July 5, 1999	PRIORITY DATE CLAIMED July 7, 1998
TITLE OF INVENTION <u>Thixotropic Formulations for Filling Hard Capsules</u>		
APPLICANT(S) FOR DO/EO/US <u>Pascal Lombardin, Jean-Louis Grossiord, Monique Seiller, Elie Leverd, Eric Goutay, and Joël Bougaret</u>		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<ol style="list-style-type: none"> <li><input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li><input type="checkbox"/> This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).</li> <li><input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).</li> <li><input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input checked="" type="checkbox"/> has been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li><input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).</li> <li><input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))             <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau).</li> <li>b. <input checked="" type="checkbox"/> have been communicated by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li><input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li><input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</li> <li><input type="checkbox"/> An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol>		
Items 11 to 16 below concern document(s) or information included:		
<ol style="list-style-type: none"> <li>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.</li> <li><input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>14. <input type="checkbox"/> A substitute specification.</li> <li>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>16. <input type="checkbox"/> Other items or information:</li> </ol>		

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER	
097743248			
<p>17. <input checked="" type="checkbox"/> The following fees are submitted:</p> <p><b>BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :</b></p> <p>Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1000.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$860.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$710.00</p> <p>International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$690.00</p> <p>International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00</p>		CALCULATIONS PTO USE ONLY	
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>		\$ 860.-	
<p>Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).</p>		\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	- 20 =		X \$18.00
Independent claims	- 3 =		X \$80.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		+ \$270.00	\$
<b>TOTAL OF ABOVE CALCULATIONS =</b>		\$	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.		\$	
<b>SUBTOTAL =</b>		\$	
<p>Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).</p>		\$	
<b>TOTAL NATIONAL FEE =</b>		\$	
<p>Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property</p>		\$	
<b>TOTAL FEES ENCLOSED =</b>		\$ 860.-	
		Amount to be refunded: \$	
		charged: \$	
<p>a. <input checked="" type="checkbox"/> A check in the amount of \$ 860.00 to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-3520. A duplicate copy of this sheet is enclosed.</p>			
<p><b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b></p>			
<p>SEND ALL CORRESPONDENCE TO:</p> <p>The Firm of Hueschen and Sage 715 The "H" Building 310 East Michigan Avenue Kalamazoo, Michigan 49007 616 382-0030</p>			
			
<p style="text-align: center;">25666 PATENT TRADEMARK OFFICE</p>			
<p><i>G. Patrick Sage</i> SIGNATURE: G. PATRICK SAGE NAME 37,710 REGISTRATION NUMBER</p>			

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

\* \* \* \* \*

Applicants: Pascal Lombardin, Jean-Louis Grossiord, Monique Seiller, Elie Leverd, Eric Goutay, and Joël Bougaret

Serial No.: 09/ Filed : January 5, 2001

Title : Thixotropic Formulations for Filling Hard Capsules

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HON. COMMISSIONER OF PATENTS AND TRADEMARKS  
WASHINGTON, D.C. 20231

PRELIMINARY AMENDMENT

As soon as the Serial Number and the Filing Date have been accorded the above-identified application, please enter the following amendment:

IN THE CLAIMS:

Claims 2-10, line 1 of each: Change "Compositions" to --A composition--.

Claim 3, line 1: Delete "or 2".

line 2: Delete the line and insert --which contains--.

Claim 5, line 1: Delete "or 4".

Claim 6, line 1: Change "one of claims 3 to 5" to --claim 3--.

Claim 8, line 1: Change "one of claims 3 to 7" to --claim 3--.

Claim 10 lines 1 and 2: Change "one of the preceding claims" to --claim 1--.

R E M A R K S

A few constructive editorial changes have been made in the claims to bring them somewhat more into line with US practice and requirements.

Entry of the amendments and favorable action on the merits are all hereby respectfully solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: G. Patrick Sage  
G. PATRICK SAGE (37,710)

Dated: January 5, 2001.  
Customer No. 25,666  
715 The "H" Building  
310 East Michigan Avenue  
Kalamazoo, MI 49007  
616 382-0030 GPS:ju

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**"Thixotropic formulations for filling hard capsules"**

5       The present invention relates to thixotropic pharmaceutical or veterinary, dietary or cosmetic compositions containing one or more active substances intended for filling capsules with a hard casing, called hard capsules, at room temperature.

10      The term "room temperature" is understood to mean a temperature substantially between 15 and 30°C.

15      Two types of capsules are used for medicinal products intended for oral, rectal or vaginal administration, namely capsules with a soft case and capsules with a hard case.

20      Individual liquid or pasty pharmaceutical compositions are conventionally presented in soft capsules. However, the process for manufacturing soft capsules requires the use of complex plants and specialized custom molders, so that the use of hard capsules may, for economic reasons, be preferred.

25      Hard capsules are conventionally used for packaging solid substances such as powders and granules. In some cases, filling hard capsules with solid substances poses certain technical problems such as, on the one hand, the generation of contaminating dust when handling active and toxic substances (anticancers, hormones) - something which may prove to be particularly dangerous - and, on the other hand, the 30 nonuniform filling from one hard capsule to another when the active substance or substances are lightly dosed.

35      This is why a solid active substance may be combined with a liquid vehicle before being packaged in hard capsules (US H 672).

The use of a liquid vehicle for the filling of hard capsules also raises problems, since the liquid can flow out between the body and the top of the hard

capsule. Leaks are generally avoided by sealing the hard capsules (EP 488 181 and WO-91/02520). This sealing operation requires a particular know-how and an additional step incurring a not insignificant  
5 additional cost.

An alternative to sealing the hard capsules has been proposed. It consists in filling the hard capsules with a composition containing the active principle in the dissolved or dispersed state. This same composition  
10 is liquid or pasty and of low viscosity during the filling and it then thickens inside the hard capsules.

According to a first filling mode, called "hot filling", the composition, which is pasty at room temperature, is thinned by heating (EP-49 909). This  
15 method cannot be applied to heat-sensitive active principles such as certain anticancer agents, vitamins and antibiotics.

According to a second filling mode, called "room-temperature filling", GB-1 590 864 provides  
20 compositions such that

25           - their viscosity at  $20 \pm 1^\circ\text{C}$  is between 500 and 5000 mPa.s, preferably between 1000 and 3000 mPa.s, measured at 450 revolutions per minute on a Haake viscosimeter,

and such that

30           - their surface tension is greater than 20 dynes/cm, preferably greater than 30 dynes/cm.

However, GB-1 590 864 does not specify what the viscosity of the compositions at rest must be.

35           Moreover, a third filling mode, combining the first two, has been described in EP-49 909. According to this method, a shear-thinning composition, containing liquid paraffin, hydrogenated castor oil and colloidal silica, is heated to  $40^\circ\text{C}$ .

The Applicant has demonstrated that the shear-thinning nature of the compositions for filling hard capsules of the prior art, although necessary for ensuring proper filling of the hard capsule,  
5 nevertheless proves to be insufficient.

This is because it is also imperative to check that the formulation at rest in the hard capsule restructures sufficiently strongly and above all sufficiently quickly, after filling, to avoid any  
10 leakage between the two parts of the hard capsule.

It is therefore absolutely essential for the consistency of the composition at rest to be sufficient to avoid any flow of the composition between the two parts of the hard capsule.

15 Among the raw materials that are used in conventional filling compositions are polyethylene glycols. Polyethylene glycols are intended to dissolve the water-soluble active principle of the filling composition, by virtue of their hydrophilic properties  
20 (EP-276 116, EP-488 181 and EP-49 909).

It has been found that the incorporation, as continuous phase, of polyethylene glycols, and more particularly of polyethylene glycols of low average molecular masses, in the filling composition may pose  
25 serious physicochemical interaction problems and therefore stability problems.

In particular, these polyethylene glycols are hygroscopic and attract water from the gelatin into the continuous phase making the case brittle and weak  
30 during storage.

The filling compositions of the present invention are advantageously free of any polyethylene glycol, and in particular of polyethylene glycol of low average molecular mass, which would run the risk of  
35 weakening the case of the hard capsules.

The objective of the present invention is to provide compositions termed "thixotropic" compositions containing one or more active substances which allow easy filling of the hard capsules at room temperature

and which ensure the absence of leaks between the two parts of the hard capsule without it being necessary to make use of the sealing usually recommended for this type of pharmaceutical dosage form.

5       The rheological properties of the formulations of the invention ensure effective filling at room temperature and the absence of leaks from the filled hard capsules.

It will be recalled that a liquid or pasty  
10 thixotropic composition has a shear-thinning character which is manifested by a reduction in the apparent viscosity under the effect of increasing shear. Furthermore, any variation in the shear conditions causes a structural modification delayed over time.  
15 Thus, in particular a gradual, total or partial recovery in consistency is observed after the shear has stopped.

The rheological parameters chosen as being particularly representative of the consistency of the  
20 formulations are:

- the complex modulus  $G^*$ , the value of which is greater the thicker the product under study, which complex modulus is a synthesis of the elastic and viscous properties of the material, and
- the phase shift  $\delta$ , of between  $0^\circ$  and  $90^\circ$ , knowing that a phase shift of greater than  $45^\circ$  characterizes a predominantly viscous nature and, conversely, a phase shift of less than  $45^\circ$  demonstrates a predominantly elastic nature characteristic of a structured material.

The present invention relates to liquid or  
35 pasty thixotropic compositions containing one or more active substances, intended for filling hard capsules at room temperature, such that:

- their complex modulus  $G^*$  is greater than about 100 Pa,
- their phase shift  $\delta$  is less than about  $45^\circ$ ,
- their viscosity decreases with increasing shear rate,
- under the effect of a constant shear rate  $\gamma_0$ , the viscosity of the said compositions decreases in a delayed manner over time and stabilizes at the equilibrium value  $\eta_{eq}$  of between 10 mPa.s and about 10 000 mPa.s, when  $\gamma_0$  is between 100 and 1000  $s^{-1}$  and
- after making the said shear rate 0, the complex modulus and the phase shift of the said compositions resume, after a time  $t$  of less than 1 hour,  $G^*$  and  $\delta$  values of greater than about 100 Pa and of less than about  $45^\circ$ , respectively.

The compositions according to the invention are therefore defined, on the one hand, by their shear-thinning nature, that is to say that their viscosity decreases when the intensity of the shear increases and, on the other hand, by the decrease in their viscosity over time for a given shear.

The formations of the invention thus thin in the hard-capsule filling machine due to the effect of the shear induced by the agitation present from the feed hopper right to the dispensing nozzle. This property makes it particular easy to fill the hard capsules.

For each shear rate, the viscosity of the compositions of the invention decreases over time and finally stabilizes at an equilibrium value denoted  $\eta_{eq}$ .  
The compositions according to the invention have equilibrium viscosities  $\eta_{eq}$  at  $100s^{-1}$  and  $1000 s^{-1}$  of between 10 mPa.s and 10 000 mPa.s, preferably between 100 mPa.s and 1500 mPa.s. It is entirely unnecessary to

make use of a heating operation, as required in certain processes of the prior art (US-4 450 877).

The compositions according to the invention are also defined by a significant recovery in consistency 5 delayed over time.

The compositions of the invention, thinned in the hard-capsule filling machine, resume their initial consistency after a sufficient rest time, so as to avoid any risk of a leak from the full capsule.

10 The formulations according to the invention are characterized by  $G^*$  values of greater than 100 Pa, preferably greater than 1000 Pa, and/or  $\delta$  values of less than 45°, preferably less than 25°, and/or a recovery time  $t$  of less than 1 hour and preferably less 15 than 30 minutes, and/or  $\eta_{eq}$  values of between 100 mPa.s and 1500 mPa.s when the shear rate is between 100 and 1000 s<sup>-1</sup>.

Once the recovery has been completed,  $G^*_{eq}$  is greater than 100 Pa, preferably 1000 Pa, and  $\delta_{eq}$  is less 20 than 45°, preferably less than 25°.

The hard capsules used within the context of the present invention consist of gelatin, of a cellulose polymer (such as hydroxypropylmethyl cellulose) or of any other polymer capable of 25 fulfilling the use functions of gelatin in the form of a hard capsule.

According to a preferred embodiment, the thixotropic compositions of the present invention are dispersions containing a continuous liquid or pasty 30 dispersing phase, a viscosity-modulating dispersed phase in the particulate or micellar state and at least one active substance present in the dissolved and/or dispersed state.

The dispersing phases of the invention are 35 characterized by their wide polarity range in terms of hydrophilic-lipophilic balance (HLB). The raw materials used in the formulation of these dispersing phases of the invention have hydrophilic, lipophilic or amphiphilic properties of variable HLB which allow the

dissolution or dispersion of liquid and solid active principles which are themselves hydrophilic, lipophilic or amphiphilic.

The continuous phase of these compositions  
5 advantageously consists of at least one vehicle such as oils, their derivatives, and more particularly amphiphilic esters having an HLB of between 3 and 15, such as amphiphilic polyglycolized glycerides, like LABRASOL® and LABRAFIL® sold by Gattefosse.

10 The use of amphiphilic vehicles having a hydrophilic tendency represents a good alternative to the hydrophilic polyethylene glycols of the prior art. Apart from polyethylene glycols, the products conventionally used in the formulation of liquid or  
15 pasty thixotropic preparations for a hard capsule are rather lipophilic (GB-1 590 864, US-4 450 877, US-H672, EP-461 290).

The amphiphilic continuous phases having a hydrophilic tendency used within the context of the  
20 present invention, unlike the excipients of the prior art, prove to be ideally suited to hydrophilic, lipophilic or amphiphilic active principles, whether they dissolve or disperse respectively.

The viscosity-modulating dispersed phase of the  
25 compositions according to the invention may be chosen from hydrophilic or hydrophobic pyrogenic silica particles, the mean size of which may be between 5 and 50 nm, preferably between 7 and 20 nm, and the specific surface area between 10 and 450 m<sup>2</sup>/g, preferably  
30 between 70 and 410 m<sup>2</sup>/g, such as AEROSIL® sold by Degussa, and ethylene oxide and propylene oxide copolymers, such as SYNPERONIC® products sold by ICI, and mixtures thereof.

The dispersed phase combined with the  
35 continuous phase makes it possible to achieve HLB values ranging up to about 20.

The viscosity-modulating dispersed phase of the compositions according to the invention preferably

represents from 1 to 30% m/m, more preferably from 5 to 15% m/m, of the preparation.

The excipients used in the formulation of the thixotropic compositions according to the invention are chosen from pharmaceutically acceptable excipients that are inert with respect to the active substances that it is desired to formulate.

Furthermore, these excipients are chosen from excipients that are compatible with the casing of the hard capsules.

The excipients which are used in the formulation of the thixotropic compositions according to the invention are advantageously endowed with hydrophilic, lipophilic or amphiphilic properties with, for these, a variable hydrophilic-lipophilic balance (HLB), which allow the dissolution or dispersion of both hydrophilic and lipophilic active substances. The HLB of the vehicles may vary from  $4 \pm 1$  for a combination of LABRAFIL® M1944CS and AEROSIL® to  $20 \pm 1$  for a combination of LABRASOL® and SYNPERONIC®.

The compositions according to the invention contain an active substance which may be liquid or pasty but also solid, for example milnacipran hydrochloride (solubility in water of 600 g/l), baquimast (solubility in water of 0.23 g/l), nifedipine, triamterene, aluminum hydroxychloride, sodium salicylate, vancomycin, paramethadone and griseofulvin.

The hard capsules used within the context of the present invention consist of gelatin or of any other cellulose polymer capable of fulfilling the functions of the use of gelatin in the form of a hard capsule, such as hydropropylmethyl cellulose.

The invention is not limited to these examples and a person skilled in the art will be easily able to include any active substance of his choice, whether liquid, pasty or even solid, in the compositions described.

The present invention also relates to the use of the compositions described above in a cosmetic, dietary, pharmaceutical or veterinary preparation.

5 The present invention is illustrated by the following examples with reference to the appended figures:

10 • figure 1 shows the rheogram of a formulation of example 4 of the invention and the rheogram of a composition of example 5, the rheological properties of which do not meet the criteria of the invention.

15 The stress (in pascals) is plotted on the y-axis and the shear rate (in  $s^{-1}$ ) is plotted on the x-axis;

20 • figure 2 gives the time dependence of the recovery in consistency of two formulations of the invention, that of example 2 and that of example 4.

25 The complex modulus, expressed in pascals, is plotted on the y-axis and the time is plotted on the x-axis;

30 • figures 3 and 4 represent the degree of dissolution as a percentage (on the y-axis) of a formulation of example 1 and of a formulation of example 2, respectively, as a function of time (on the x-axis) expressed in hours and in minutes, representively.

EXAMPLES 1 TO 7:

35

a) Preparation of the dispersions:

Seven dispersions were prepared, each containing a continuous phase, a dispersed phase and an active phase.

The continuous phase consisted of an amphiphilic ester such as LABRAFIL M1944CS® (HLB = 4 ± 1) or LABRASOL® (HLB = 14 ± 1). It should be mentioned at this stage that the amphiphilic esters

that can be used within the context of the invention may have HLB values of between 3 and 15.

The dispersed phase was chosen from AEROSIL 200 V® (a hydrophilic pyrogenic silica),  
5 AEROSIL R 974® (a hydrophobic pyrogenic silica) and SYNPERONIC PE/F 68® (an ethylene oxide/propylene oxide copolymer having an HLB of 29 ± 1). When the dispersed phase chosen was SYNPERONIC®, the HLB of the dispersing phase increased to about 20.

10 The active substance was chosen from milnacipran hydrochloride (a solid whose solubility in water is 600 g/l) and baquimast (a solid whose solubility in water is 0.23 g/l).

15 The preparations containing pyrogenic silica as dispersed phase were obtained by gradually adding silica to the amphiphilic ester with vigorous stirring, advantageously at between 1000 and 3000 revolutions per minute. The mixture was then put under vacuum and the stirring continued after incorporating the silica until 20 homogeneous. The preparations containing SYNPERONIC® as dispersed phase were obtained by gradually adding SYNPERONIC® to the amphiphilic ester with moderate stirring, advantageously at between 400 and 800 revolutions per minute. The mixture was then put under 25 vacuum and the stirring continued until homogeneous.

Whether the preparations contained AEROSIL® or SYNPERONIC® as viscosity-modulating dispersed phase, the active substance chosen was always added to the amphiphilic ester/dispersed phase mixture at room 30 temperature with moderate stirring. The composition of each dispersion is given in detail in table I below.

**b) Rheological properties**

35 The rheological properties of the seven preparations were then studied in terms of shear thinning and of recovery in consistency.

b1) The shear thinning is characterized at 25°C in terms of flow rheology in a rotating controlled-stress rheometer (Carri-Med CSL100).

5 The "stress as a function of shear rate" rheogram is plotted for each of the dispersions. The rheogram makes it possible to check the ability of a preparation to undergo thinning when the intensity of the shear increases.

10 Since the viscosity is defined as the ratio of the stress to the shear rate, a convex curve is an expression of a decrease in the viscosity with shear rate, that is to say a shear-thinning behavior, whereas a concave curve is an expression of an increase in the viscosity with shear rate, i.e. a shear-thickening 15 behavior.

Figure 1 shows the rheogram for two dispersions, dispersion 4 and dispersion 5, the compositions of which are given in table I above. The line of the rheogram for dispersion 4, which is convex, 20 means that dispersion 4 is shear thinning and meets one of the criteria of the compositions of the invention, whereas that for preparation 5, which is concave, demonstrates its shear-thickening character.

Table I specifies the observed shear-thinning 25 or shear-thickening character in light of the rheogram for each dispersion.

The formulations were also subjected to constant shear rates of the same order of magnitude as those involved in a hard-capsule filling machine of 30 conventional type ( $100\text{ s}^{-1}$  for the lines in the machine and  $1000\text{ s}^{-1}$  for the narrowing at the exit of the injection nozzle).

For each shear rate, it may be seen that there 35 is a reduction in the viscosity over time, which finally stabilizes at an equilibrium value denoted  $\eta_{eq}$ . The results are given in table I.

The seven dispersions have equilibrium viscosities, at a shear rate of  $100\text{ s}^{-1}$  or  $1000\text{ s}^{-1}$ , of between 100 mPa.s and 5000 mPa.s.

These viscosity values consequently prove to be suitable for the automatic filling of hard capsules. It is entirely unnecessary to thin our thixotropic dispersions further by raising the filling temperature,  
5 as recommended by the authors of patent US-4 450 877.

b2) The rheological conditions relating to the resumption of thixotropy, and which guarantee that there are no leaks long term, were determined at 25°C, in dynamic rheology, in a controlled-stress Couette-type rotating rheometer (Carri-Med CSL 100).  
10

This mode of study, unlike flow rheology, allows the consistency of a material "at rest" to be assessed since it is possible to apply appreciably smaller strains to the material than in flow.

15 The seven dispersions were presheared for 15 minutes at  $1000\text{ s}^{-1}$ .

The parameters used to characterize the recovery in consistency are the magnitude of the recovery (expressed as a percentage), the complex modulus  $G^*$  (in pascals) after recovery and the phase shift  $\delta$  (in degrees) 1 hour after stopping the shear and the time  $t_{50\%}$  for the recovery to reach 50% with respect to  $G^*_{eq}$ . The results are summarized in table I above.  
20  
25

The percentage recovery in consistency of the shear-thinning dispersions 1, 2, 3, 4, 6 and 7 is equal to 100%. The recovery is therefore total. The values of the  $G^*$  recovery after 1 hour are total and greater than 100 Pa in respect of preparations 1, 4 and 7, but less than 100 Pa in respect of preparations 5 and 6, which reach values of 5 and 70 Pa, respectively.  
30

After recovery,  $\delta$  is less than 25° for all the dispersions, with the exception of dispersion 5 (equal to 71°).

35 For the five shear-thinning dispersions,  $t_{50\%}$  is less than 30 minutes.

Dispersions 1, 2, 3, 6 and 7 therefore undergo rapid and total recovery in their consistency, which furthermore is considerable.

Figure 2 shows the change in  $G^*$  as a function of time for dispersions 2 and 4. It may be seen that the recovery in consistency of dispersion 2 is very rapid ( $t_{50\%} = 1$  s) and considerable (after recovery 5  $G^* = 1400$  Pa), that of dispersion 4 is slower ( $t_{50\%} = 23$  min.) and considerable (after recovery  $G^* = 900$  Pa).

**c) Hard-capsule stability study**

10

Having studied the rheological properties of the dispersions, they were dispensed into size-1 conventional-closure hard gelatin capsules at room temperature using an industrial-type filling machine. 15 The filling was carried out with a coefficient of variation in the mass of the filled hard capsule which was systematically less than 1.5%.

The filled hard capsules were stored for 12 months in an oven ( $25^\circ\text{C} \pm 2^\circ\text{C}$  and  $60\%$  RH  $\pm 5\%$  RH) in 20 order to confirm that there were no leaks and no deformation in the casing of the capsule. Only the capsules containing preparations 5 and 6 had leaks during storage.

25 **d) Hard-capsule *in vitro* release study**

In *vitro* release studies, performed in a "Dissolutest" (water at  $37 \pm 0.5^\circ\text{C}$ , 100 tpm), were carried out. The results for preparations 1 and 2 are 30 given in figures 3 and 4, respectively.

The release of milnacipran hydrochloride (a solid water-soluble active principle) is more rapid the more hydrophilic the continuous phase.

Under the operating conditions employed, 35 preparation 2 (figure 4) containing an amphiphilic ester having a hydrophilic tendency (HLB = 14) releases the active principle very much more rapidly than preparation 1 (figure 3) containing an amphiphilic ester having a lipophilic tendency (HLB = 4  $\pm$  1).

The choice of continuous phase therefore makes it possible to tailor the rate of release of the active principle.

TABLE I: COMPOSITIONS AND CRITICAL RHEOLOGICAL PARAMETERS OF THE DISPERSION EXAMPLES

E x a m p 1 e s	Formulation: Continuous phase Dispersed phase Active principle (% m/m)	Thixotropy characterization						Stability: 25 ± 2°C; 60% ± 5% RH (12 months)	
		Rheogram Shear thinning	Shear Stress $= f(\text{rate})$	$\eta_{\text{eq}}$ at 100 s <sup>-1</sup> (mPa.s)	$\eta_{\text{eq}}$ at 1000 s <sup>-1</sup> (mPa.s)	Extent of the recovery (%)	G* after recovery (Pa)	δ after recovery (*)	
1	LABRAFIL M1944CS® AEROSIL 200V® Milnacipran hydrochloride	90% 10% 96%	Shear-thinning 4%	710	360	100	3100	5	21 s Stable
2	LABRASOL® AEROSIL 200V® Milnacipran hydrochloride	94% 6% 96%	Shear-thinning 4%	390	190	100	1400	8	1 s Stable
3	LABRASOL® SYNPERNIC PE/F68 ® Milnacipran hydrochloride	88% 12% 93%	Shear-thinning 7%	810	600	100	2100	17	12 min Stable
4	LABRAFIL M1944CS® AEROSOL R974® BAQUIMAST®	90% 10% 95%	Shear-thinning 5%	1020	980	100	900	12	23 min Stable
5	LABRASOL® AEROSIL R974® Milnacipran hydrochloride	90% 10% 96%	Shear-thickening 4%	510	1100	—	5	71	— Leaks
6	LABRAFIL M1944CS® AEROSIL 200V® Milnacipran hydrochloride	96% 4% 96%	Shear-thinning 4%	140	110	100	70	21	6 s Leaks
7	LABRASOL® SYNPERNIC PE/F68 ® Milnacipran hydrochloride	70% 30% 96%	Shear-thinning 4%	4800	2300	100	18 780	12	12 min Stable

**CLAIMS**

1. Liquid or pasty thixotropic compositions containing one or more active substances, intended for filling hard capsules at room temperature, such that:

- their complex modulus  $G^*$  is greater than about 100 Pa,
- their phase shift  $\delta$  is less than about  $45^\circ$ ,
- their viscosity decreases with increasing shear rate,
- under the effect of a constant shear rate  $\gamma_0$ , the viscosity of the said compositions decreases in a delayed manner over time and stabilizes at the equilibrium value  $\eta_{eq}$  of between 10 mPa.s and about 10 000 mPa.s, when  $\gamma_0$  is between 100 and 1000  $s^{-1}$  and
- after making the said shear rate 0, the complex modulus and the phase shift of the said compositions resume, after a time  $t$  of less than 1 hour,  $G^*$  and  $\delta$  values of greater than about 100 Pa and of less than about  $45^\circ$ , respectively.

2. Compositions according to claim 1, characterized in that:

$G^*$  is greater than 1000 Pa, and/or  
 $\delta$  is less than  $25^\circ$  and/or  
 $\eta_{eq}$  is between 100 and 1500 mPa.s when  $\gamma_0$  is between 100 and 1000  $s^{-1}$  and/or  
 $t$  is less than 30 min.

3. Compositions according to claim 1 or 2, characterized in that they are preparations containing a continuous dispersing phase, a dispersed phase and at least one active substance.

4. Compositions according to claim 3, characterized in that the continuous phase consists of at least one vehicle such as amphiphilic esters having an HLB of between 3 and 15 and more particularly polyglycolized glycerides.

5. Compositions according to claim 3 or 4, characterized in that the dispersed phase is chosen from hydrophilic or hydrophobic pyrogenic silica particles and ethylene oxide/propylene oxide copolymers, the latter making it possible to achieve, when combined with the continuous phase, HLB values ranging up to about 20.

6. Compositions according to one of claims 3 to 5, characterized in that the active substance is liquid, pasty or solid.

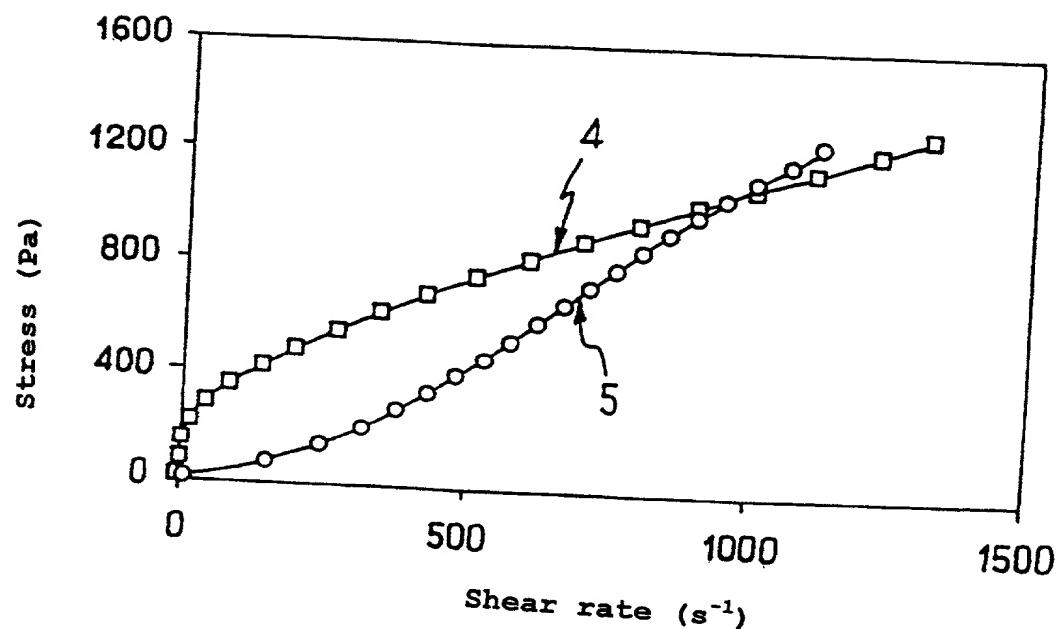
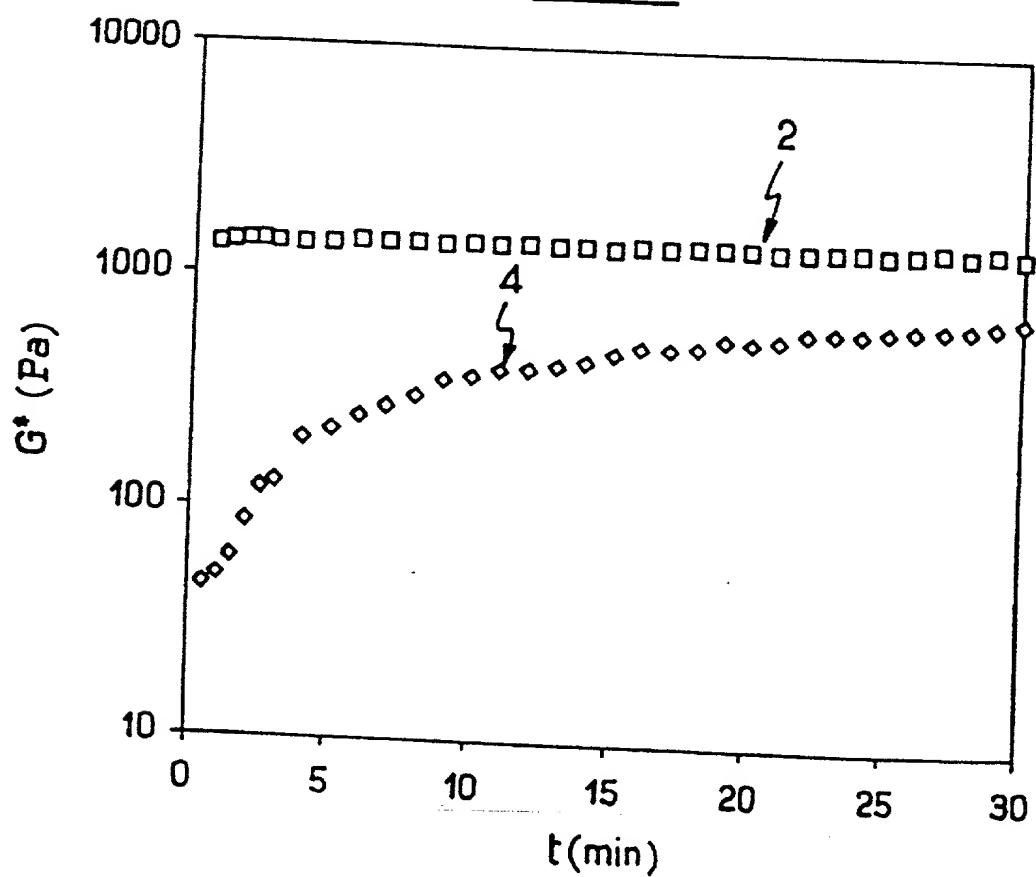
7. Compositions according to claim 6, characterized in that the active substance is chosen from milnacipran hydrochloride, baquimast, nifedipine, triamterene, aluminum hydroxychloride, sodium salicylate, vancomycin, paramethadone and griseofulvin.

8. Compositions according to one of claims 3 to 7, characterized in that the dispersed phase of the preparations according to the invention represents 1 to 30% m/m of the preparation.

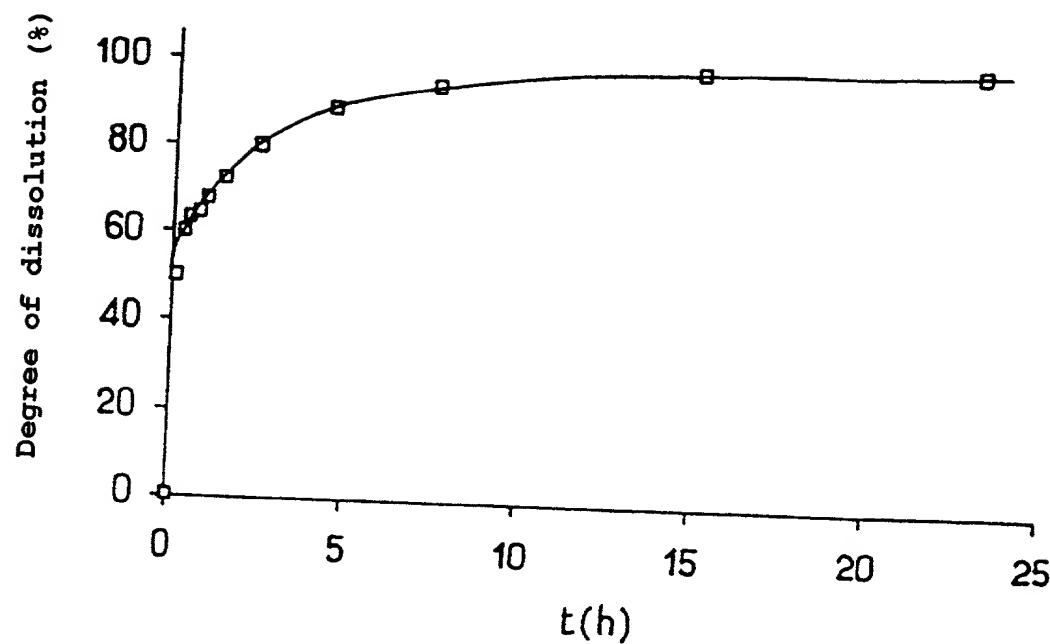
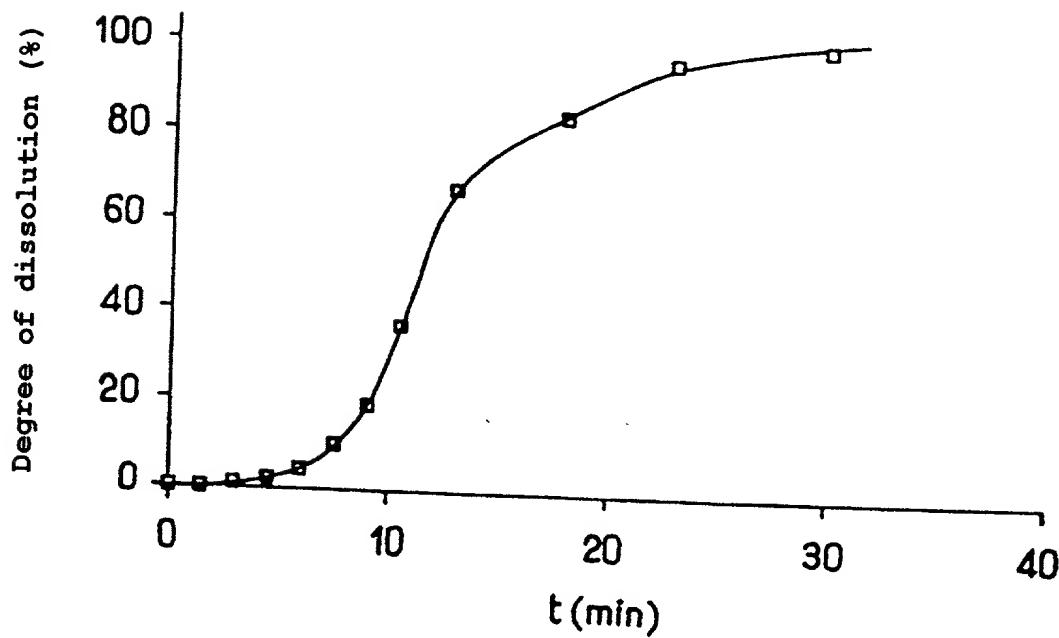
9. Compositions according to claim 8, characterized in that the dispersed phase of the dispersions according to the invention represents from 5 to 15% m/m of the preparation.

10. Compositions according to one of the preceding claims, characterized in that the hard capsules consist of gelatin or of any other cellulose polymer capable of fulfilling the functions of the use of gelatin in the form of a hard capsule, such as hydroxypropylmethyl cellulose.

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FIG. 1FIG. 2

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FIG. 3FIG. 4

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## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled.

#### **THIXOTROPIC FORMULATIONS FOR FILLING HARD CAPSULES**

the specification of which (check one of the following)

is attached hereto;  was filed on \_\_\_\_\_ as Application Serial

No. \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable)

was filed as PCT International Application No. PCT/FR99/01614

on 05 JULY 1999 and was amended under PCT Article 19 on \_\_\_\_\_ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
98 08664 (Number)	FRANCE (Country)	07/07/98 (Day/Month/Year Filed)	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

PCT/FR99/01614

05 JULY 1999

Pending

(Application Serial No.)

(Filing Date)

(Status)

(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)

(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number*)

GORDON W. HUESCHEN, Reg. No. 16,157

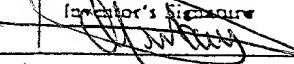
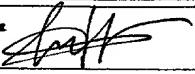
G. PATRICK SAGE, Reg. No. 37,710

Send Correspondence to:

The Firm of Gordon W. Hueschen  
715 The "H" Building  
310 East Michigan Avenue  
Kalamazoo, MI 49007  
UNITED STATES OF AMERICA

Direct Telephone Calls to: (name and telephone number) 616-382-0030

FULL NAME OF SOLE OR FIRST INVENTOR <u>LOMBARDIN Pascal</u>	INVENTOR'S SIGNATURE	DATE <u>Feb. 7, 2001</u>
RESIDENCE <u>SAINT-MAURICE - FRANCE</u>	<u>FRX</u>	CITIZENSHIP <u>FRANCE</u>
POST OFFICE ADDRESS <u>6 Rue Adrien Damalix - 94410 SAINT-MAURICE - FRANCE</u>		
FULL NAME OF SECOND JOINT INVENTOR, IF ANY <u>GROSSIORD Jean-Louis</u>	INVENTOR'S SIGNATURE	DATE <u>Feb. 7, 2001</u>
RESIDENCE <u>SAINT-GERMAIN-LES-CORBEIL - FRANCE</u>	<u>FRX</u>	CITIZENSHIP <u>FRANCE</u>
POST OFFICE ADDRESS <u>9 Square P. Ronsard - 91250 SAINT-GERMAIN-LES-CORBEIL - FRANCE</u>		
FULL NAME OF THIRD JOINT INVENTOR, IF ANY <u>SETILLER Monique</u>	INVENTOR'S SIGNATURE	DATE <u>Feb. 7, 2001</u>
RESIDENCE <u>SCEAUX - FRANCE</u>	<u>FRX</u>	CITIZENSHIP <u>FRANCE</u>
POST OFFICE ADDRESS <u>9 Avenue Fontenelle - 92330 SCEAUX - FRANCE</u>		

Full Name of Fourth Joint Inventor, if any <u>LEVERD Elie</u>	Inventor's Signature 	Date Feb. 7, 2001
Residence <u>CASTRES - FRANCE</u>		Citizenship <u>FRANCE</u>
Post Office Address <u>20 Chemin de Cazers-Bas - 81100 CASTRES - FRANCE</u>		
Full Name of Fifth Joint Inventor, if any <u>GOUTAY Eric</u>	Inventor's Signature 	Date Feb. 7, 2001
Residence <u>LAUZERVILLE - FRANCE</u>		Citizenship <u>FRANCE</u>
Post Office Address <u>36 Les Côteaux de Marrast - 31650 LAUZERVILLE - FRANCE</u>		
Full Name of Sixth Joint Inventor, if any <u>BOUGARET Joel</u>	Inventor's Signature 	Date Feb. 7, 2001
Residence <u>LANTA - FRANCE</u>		Citizenship <u>FRANCE</u>
Post Office Address <u>Rue de la Mairie - 31570 LANTA - FRANCE</u>		